REMARKS

Claims 1, 5, 8-19, 22, 30, 35 and 36 were pending. Claims 1, 5, 8-19, 22, 30, 35 and 36 are rejected. Claim 19 is canceled herein. Claims 1, 8, 14-18, 30 and 35 are amended herein. No new matter is introduced by these amendments, and entry of the amended claims is requested.

Priority

On page 2 of the Office Action mailed March 25, 2008, the Examiner states that "the current application filed on May 20, 2005 is a 371 of PCT/US05/14210 filed April 26, 2006." Applicants assume that the Examiner meant "April 26, 2005." The Examiner requests that Applicants review the claim of priority to earlier filed provisional applications because the information provided is not consistent with the PTO data base.

Applicants have reviewed the PTO database and all the related papers, including the Certified Copies of the provisional applications submitted with the PCT file, the application cover sheet, and the Declaration filed in the instant application, and is unable to find any such inconsistencies except in the citation of the PCT application in the formal style as "PCT/US2005/014210" or the informal style as "PCT/US05/14210." Hence, Applicants respectfully request that the Examiner clarify the nature of the inconsistencies so that they may be corrected.

Objections regarding informalities

On pages 2-3 of the Office Action, the Examiner objects to informalities. In particular, the Examiner requests the full spelling of "PF-4". Applicants have made this amendment. The Examiner also notes that Chrohn's disease was misspelled. This has been corrected. Hence, Applicants have addressed the objections which may now be withdrawn.

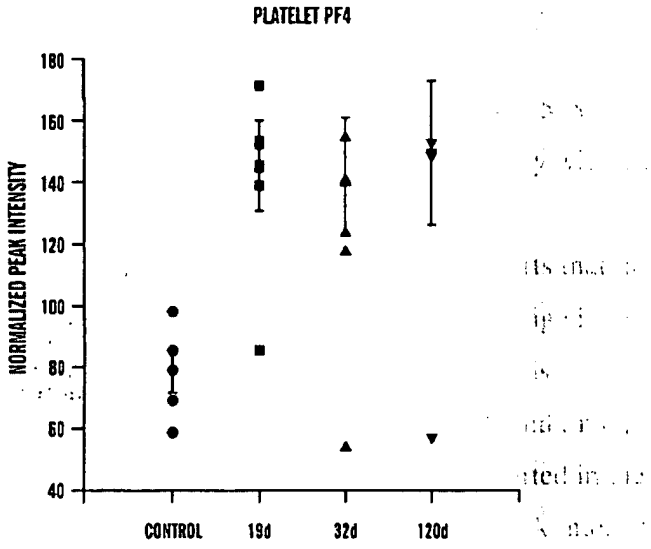
Double patenting

The Examiner, on page 3 of the Office Action, issues a provisional obviousness-type double patenting rejection over claims 5-16 and 24-27 of co-pending application Ser. No. 11/304,384. Applicants traverse the rejection, but respectfully request that the Examiner hold this rejection in abeyance as the patentable distinctions between the two claim sets may become more apparent as prosecution progresses, or until one set of claims is deemed allowable.

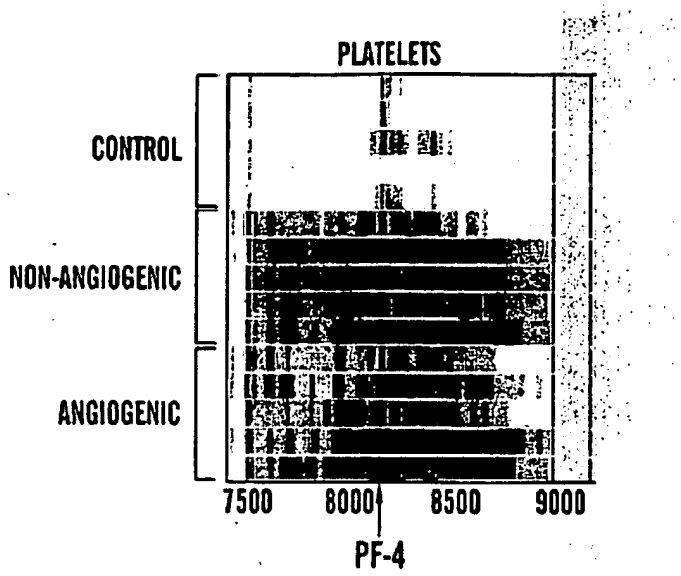
Rejections under 35 U.S.C. § 112, first paragraph

On page 4 of the Office Action, the Examiner rejects claims 1, 5, 8, 9-19, 22, 30, and 35-36 under 35 U.S.C. § 112, first paragraph, "as failing to comply with the enablement requirement." Applicants traverse the rejection.

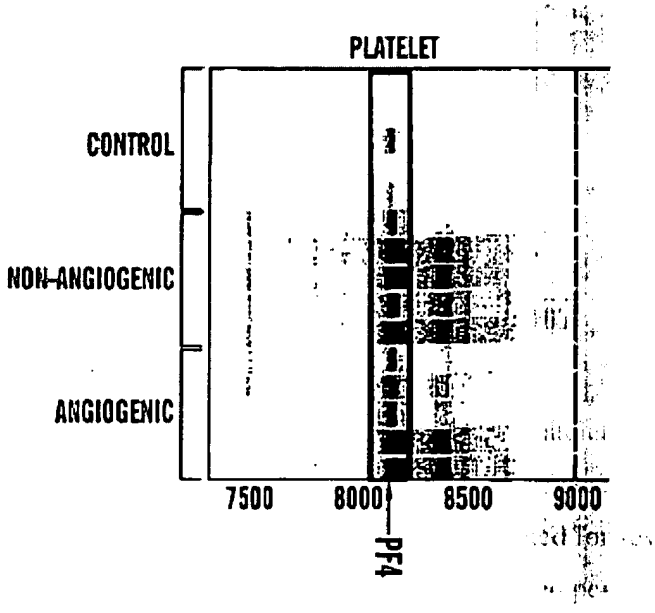
More specifically, on page 7 of the Action, the Examiner asserts that there is insufficient enablement because there are no working examples regarding the change in level of PF-4 between a first and second time point as indicative of angiogenic disease. The amended claim clarifies that an increase in the level of PF-4 from the first to the second time point is indicative of the presence of a tumor in the individual. This is adequately supported in the specification, for example, at Figure 22C which shows a plot of the normalized PF4 peak intensity in platelets of an established model of tumor-bearing mice at 0 (control) 19 days, 32 days and 120 days of growth, indicating that platelet PF4 levels increased over the time course studied:



Similarly, Figure 17 shows a marked increase in PF-4 comparing control and 30-day time points for human liposarcoma-bearing SCID mice:



Additionally, Figure 29 presents a representative analysis of platelet protein profiles of tumor-bearing mice. Spectra from healthy mice ("Controls"), and mice bearing tumor xenografts are displayed in gel view. Differential expression patterns were detected for several peptides. (Abscises: Relative MW computed from m/z value, Ordinate: Identified peptide confirmed by immunodepletion or immunoprecipitation, Intensity of bands correlates with relative expression profile of the protein.):



Clearly, as shown in these figures and taught in the specification, e.g., at [0249]:

> "regulators of angiogenesis were significantly ***increased*** in platelets from mice bearing non-angiogenic, dormant, microscopic-sized liposarcoma (FIG. 29). The platelets associated proteins were taken up in a selective and quantifiable manner, clearly showing ***increased*** concentrations of ... platelet factor 4 in the platelet lysates ... Platelets maintain high concentrations of sequestered angiogenesis regulatory proteins for as long as the tumor is present." (Emphasis added.)

The foregoing also provides comparisons between the level of PF-4 at a first time point and a second time point, and both show and discuss a change (increase) in the level of PF-4 between a first time point (0) and a second time point (e.g., 19 days, 30 days, etc.).

The Examiner asserts that Applicants "do not relate PF-4 directly to cancer in general, breast cancer or to the tumor suppressor gene BRCA1." Office Action at page 7. The foregoing discussion illustrates a direct correlation between PF-4 and cancer, however. The support for and importance of the present invention as a method of early diagnosis in those at risk for cancers is also stated eloquently in the application at, for example [0270]:

> We have shown that the process of platelet uptake of angiogenesis regulators is highly specific, reflects the tumor status, i.e dormancy vs clinical expansion, and occurs well in advance of clinically detectable tumors. We propose that this novel compartment in the systemic circulation is superior to plasma and serum analysis of angiogenic markers, and provides a stable, sensitive and reliable method for very early cancer diagnosis. A "platelet angiogenesis proteome" may be used as an early register of tumor angiogenic switch, in much the same way that a lipid profile is used to identify patients at risk for artherosclerosis and myocardial infarction. This forecasting biomarker may be to screen patients at risk for developing cancer. Used in conjunction with other biomarkers ... we may be able to diagnose cancer recurrence years in advance of clinical symptoms, or improve the monitoring of women with BRCA cancer gene mutation and at high risk of developing breast cancer.

In other words, the specification teaches that PF-4 is increased in the platelets of individuals bearing tumors, and teaches that by monitoring the levels of PF-4 in the platelets of women at risk for breast cancer, tumors may be detected earlier, perhaps before other symptoms or markers are detected.

The Examiner also posits that the claims are not enabled because Applicants does "not provide examples where the second time point is at least 6 months, 10 months or one year after the first time point with regard to PF-4." Such examples are surely not required for one of

ordinary skill in the art. There is no further experimentation required in measuring the level of PF-4 at day 0 or day 19, which is clearly exemplified as discussed above, than there is at day 365. Moreover, the Examiner acknowledges the "art-recognized method of monitoring patients' health parameters taken at one time point to those taken at a second time point." Office Action at page 9.

The Examiner also challenges the enablement of claims 35 and 36 in which other angiogenesis regulators are monitored in addition to PF-4. These claims are fully enabled to one of ordinary skill in the art in light of the present specification. For example, Figures 16-18 show protein expression maps in which PF-4 and two additional angiogenesis regulatory proteins, VEGF and PDGF, increased after tumor implantation:

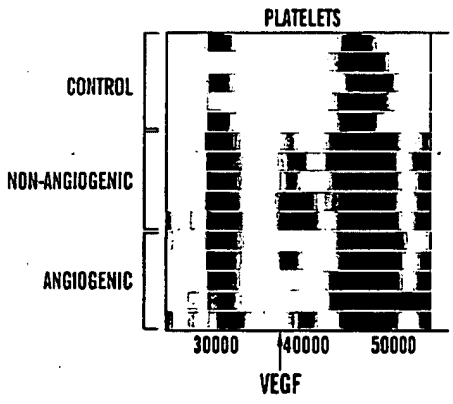


Fig. 16

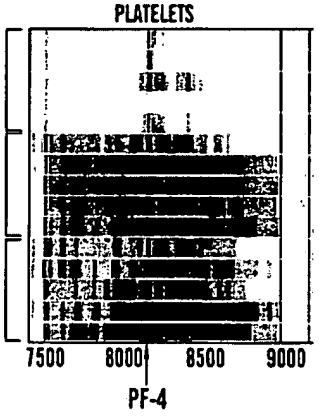


Fig. 17

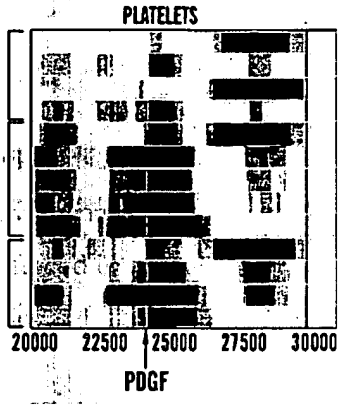


Fig. 18

Similarly, Figures 22A and 22C show that PF-4 and the additional angiogenesis regulatory protein, CTAPIII, both increased after tumor implantation:

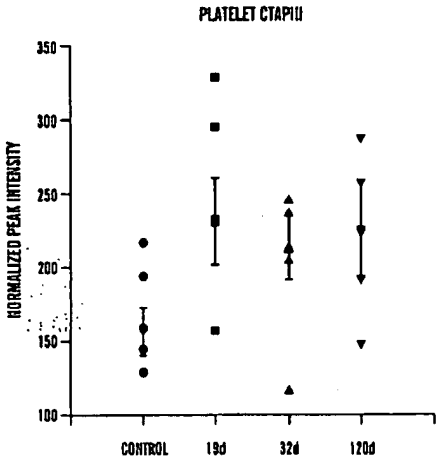


Fig. 22A

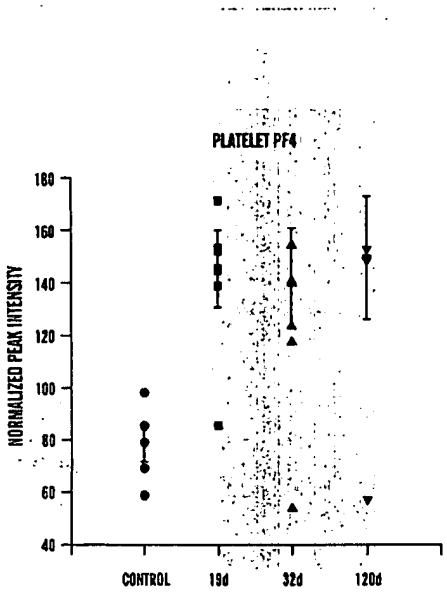


Fig. 22C

In additional, Figures 29A-29H compare levels of PF-4 (Fig. 29A) and PDGF (Figs. 29Band 29G), VEGF (Figs. 29C and 29F), Endostatin (Figs. 29D and 29H), bFGF (Fig. 29E). Moreover, these figures reflect various different methodologies that may be employed to analyze the level of the angiogenis regulatory protein.

Apart from these specific figures, there is also ample description in the specification relating to the changes in the levels of the angiogenic regulatory proteome in tumor-bearing mice, in which "VEGF, bFGF, PDGF, endostatin, angiostatin, tumstatin and other regulators of angiogenesis were significantly increased in platelets from mice bearing non-angiogenic, dormant, microscopic-sized liposarcoma ... The platelets associated proteins were taken up in a selective and quantifiable manner, clearly showing increased concentrations of VEGF, bFGF, PDGF, and platelet factor 4 in the platelet lysates."

In view of the foregoing, Applicants respectfully suggest that one of ordinary skill in the art, in light of the specification, is well enabled to compare levels of platelet-derived PF-4 and other angiogenesis regulatory proteins. Applicants request that the § 112 rejections be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

On page 8 of the Office Action, the Examiner rejects claim 30 under 35 U.S.C. § 112, second paragraph "as being indefinite." Applicants have amended claim 30, rendering this

rejection moot. The Examiner rejects claim 8 as unclear regarding "the presence of at least one angiogenic regulator." Applicants have amended claim 8 to recite PF-4, such that this claim further limits the steps of analyzing platelets in claim 1. Hence, Applicants request that these rejections be withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner, on page 9 of the Office Action, rejects claims 1, 5, 8, 12 and 13, under 35 U.S.C. § 103(a) "as being unpatentable over Komurasaki et al. (US 5,847,084)." Applicants traverse the rejection. More specifically, the Examiner asserts that "it would have been obvious to ... modify the methods of isolating platelets and PF-4 as disclosed by Komurasaki et al., based upon the art-recognized method of monitoring patients' health parameters taken at one time point to those taken at a second time point."

The present invention provides for a method for the early detection of a tumor-associated disease or disorder in an individual by isolating platelets from said individual at a first time point and analyzing the platelets for the level of PF-4, isolating platelets from said individual at a second time point and analyzing those platelets for the level of PF-4, then comparing the levels of PF-4 from the first time point to the second time point, wherein an increase in the level of PF-4 in the platelets from said second time point is indicative of the presence of a tumor in the individual.

Although the '084 patent relates to processes for purifying PF-4, there is nothing in that reference suggesting that the PF-4 in platelets from an individual may be monitored as a means for early indication of a tumor in that individual. In other words, there is nothing in the '084 patent that suggests an increase in platelet PF-4 is indicative of possible tumor development. Indeed, in teaching that "PF4 was reported to elicit angiogenesis ***inhibitory*** activity" and "PF-4 is effecting for the ***suppression*** of malignant tumor cells," (col. 1, lines 62-66) (emphasis added) the '084 patent teaches away from the results presented in the instant application: that platelet PF-4 increases in the presence of a tumor, and remains increased as long as the tumor is present. Hence, this reference does not support a § 103 rejection, and Applicants respectfully suggest that it be withdrawn.

CONCLUSION

For at least the reasons set forth above, Applicants respectfully submit that this application is in condition for allowance. Favorable consideration and prompt allowance of the claims are earnestly requested. The Commissioner is hereby authorized to charge any payment deficiency to Deposit Account No. 50-0850 referring to Attorney Docket No. 701039-055264.

Should the Examiner have any questions that would facilitate further prosecution or allowance of this application, the Examiner is invited to contact the Applicant's representative designated below.

Respectfully submitted,

Date: September 24, 2008

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